REMARKS

Claims 159, 161, 162, 163, 170 to 178, 180 to 191, 193, 194, 195, 198 to 202, 222 to 255 are pending in the application. Claims 177, 178, 181, 182, 183, 184, 185, 186, 190, 191, and 195 have been withdrawn from consideration.

35 USC § 102

Claims 163, 170 to 176, 180, 199 to 202, 222 to 223, 226 to 255 stand rejected as being anticipated by US 6,093,693, of Julius *et al.*

Applicants note that this rejection includes several claims dependent on an independent claim not included in the rejection, and Applicants thus request clarification of the claims that are intended to be rejected under 35 USC § 102. In any event, Applicants respectfully submit, for the reasons set out below, that none of the currently pending claims is sufficiently broad to encompass subject matter disclosed by Julius *et al.*

It is alleged in the outstanding action that the teachings of Julius *et al.*, which guide the skilled person to orally administer CD14 to an infant, as by means of infant formula, would fall within the scope of these claims.

Julius *et al.* teach that CD14 stimulates B cells. In the context of this function, various routes of administration are taught, so as to bring the CD14 into contact with B cells. For example, oral administration is suggested for administration to infants so as to potentiate the development of the neonatal immune system. The upper gastrointestinal tract of an infant does not present the hostile environment of the mature tract of an adult, and so the ability of CD14 to stimulate B cells suggests the possible administration by this route to infants. (column 14, line 66 to column 15, line 2; column 18 lines 2 to 5)

Applicants are aware of no teaching in the art, even today, that demonstrates the *induction* of expression of defensins in neonates. Nor have Applicants found any

showing in any of the art of record that administering CD14 orally to an infant would stimulate expression of a defensin. (By these statements, Applicants are not representing that a thorough search and review of the art with respect to this issue has been conducted.) There is thus no suggestion in the prior art of record of exposing epithelial cells to CD14 that would lead to expression of defensins.

The ability of CD14 to stimulate B cells also suggests a role for CD14 in vaccinating mammals, and thus suggests routes of administration for such indication: "intravenous, subcutaneous, intramuscular, intraventricular, intracranial, intracapsular, intraspinal, intracistemal, intraperitoneal, or oral administration." (column 18, lines 5 to 11 of Julius *et al.*) The document gives no indication that a vaccine was actually synthesized and administered to a mammal.

In this context, the skilled person skilled would understand that mammals past the neonate stage of development would be subject of vaccination, and that it is actually B-2 cells that would be the target of the administered CD14. B-2 cells are located in the spleen, lymph nodes and peripheral blood, and so the skilled person would administer the CD14 to the bloodstream, and this would not be by means of oral administration despite this route being listed as one of ten mentioned in the reference. For the convenience of the examiner, copies of four references[1] are enclosed as an Appendix to this response, which references establish (see highlighted areas of the references) the location of B cells that would be targeted during a vaccination process.

Applicants thus respectfully submit that Julius *et al.* do not disclose subject matter falling within the claims as currently presented, i.e., *stimulating* expression of a defensin by *directly exposing epithelial cells* to CD14.

---

[1] Herzenberg *et al.*, 1993. B-cell lineages exist in the mouse. *Immunology Today* **14(2)**:79-83; Kantor *et al.*, 1993. Origin of murine B cell lineages. *Annu. Rev. Immunol.* **11**:501-538; and Hardy *et al.*, 1994. Distinctive developmental origins and specificities of murine CD5$^+$ B cells. *Immunological Reviews* **137**:91-118.

35 USC § 103

Claims 159, 161 to 163, 187 to 189, 193, 194, 198, 224, 225 and 228 to 255 have been rejected as being obvious in view of Diamond *et al.* (PNAS **93**, 5156-5160, 1996) and Julius *et al.*

The background section of the specification of this application summarizes the state of the art with respect to the role of CD14 in mediation of cellular responses involving CD14. Goyert, in WO 93/19772 entitled "A novel therapy for treating sepsis using a soluble form of recombinant CD14 myelomonocytic antigen" provides a similar summary, and another such summary is given by Juan *et al.* in WO 96/20957.

Without repeating these extensive summaries here, it can be stated that these references describe the role of the CD14, be it membrane-bound CD14 or soluble CD14, as involving partnering with LPS.

There is nothing in Diamond *et al.* that contradicts this widely accepted mechanism of CD14-mediated responses, even as implicitly acknowledged in the outstanding rejection which states "Diamond can mediate lipopolysaccharide-stimulated responses in epithelial cells." There is no teaching by Diamond *et al.* to administer CD14 so as to directly expose epithelial cells thereto with the expectation of stimulating expression of defensins. As set out in greater detail below, the prior art, and Diamond *et al.* in particular, teach that sCD14 binds to LPS. Further, insofar as Diamond *et al.* teach that binding of LPS and endogenous epithelial CD14 stimulates defensin production by epithelial cells, this reference teaches away from Applicants' invention by suggesting that administration of exogenous CD14, by binding to LPS would inhibit binding of LPS with endogenous epithelial CD14 so as to reduce stimulation of defensins by such binding of LPS with endogenous CD14 binding. (Applicants' note, however, that Pugin *et al.*, discussed below, suggest the possibility of sCD14-LPS complexes which interact with epithelial cells to cause their activation.)

Diamond *et al.* state that it was known prior to their work that "certain invertebrate epithelial cells can recognize microorganisms and mount a direct defense response, characterized by synthesis of a variety of antibiotic proteins and peptides." The authors then state that "no comparable response has been characterized for mammalian epithelial cells." (Column 1, last five lines of the first paragraph of text of the article.) Diamond *et al.* state that the production of antibiotic peptides is a widespread mechanism of host defense in the animal kingdom, but that "factors that govern the regulated expression of mammalian antibiotic peptides are poorly understood." Upregulation of genes encoding antimicrobial peptides had been observed for insect epithelial cells responding to bacterial components, and Diamond *et al.* "sought evidence for an analogous host defense response in mammalian airway cells." The authors then summarize the results of their work: "The bacterial membrane component lipopolysaccharide (LPS) was found to be a potent stimulus for the epithelial cell response. The mechanism by which the TECs (tracheal epithelial cells) *recognize LPS* was also addressed in these studies." (Emphasis added; paragraph bridging the columns on page 5156, and following paragraph.)

Diamond *et al.*, based on their understanding that "the CD14 molecule is a major mammalian receptor for LPS", and aware that "CD14 exists in two forms, a [GPI]-anchored membrane form characterized from macrophages and a soluble form" and that "the soluble form found in serum can mediate LPS-stimulated responses in endothelial and epithelial cells," conducted experiments to determine the role of CD14 in mediating the induction of TAP in cultured TECs. (Paragraph bridging pages 5157 and 5158) Based on the observation "that serum augments a response of TECs to LPS," and in all other experiments the culture contained no serum, Diamond *et al.* concluded that "induction of TAP does *not* involve serum-derived (i.e., soluble) CD14." Based on further experiments, Diamond went on to "conclude that (membrane-bound) CD14 of epithelial cell origin mediates the observed response of TECs *to LPS*." (Emphasis added, paragraph bridging pages 5157 and 5158)

Taken in the context of the understanding at the time, construing the statement of Diamond *et al.* that "the soluble form found in serum can mediate LPS-stimulated responses in endothelial and epithelial cells," to mean that Diamond *et al.* were of the view that soluble CD14 induces TAP production, is to turn this statement on its head.

In fact, the statement of Diamond *et al.* is itself a summary of what was known at the time as referred to in the following documents:

Goldblum, S.F., Brann, T.W., Ding, X., Pugin, J & Tobias, P.S. (1994) *J. Clin . Invest.* **93**, 692-702.

Read, M.A., Cordle, S.R., Veach, R.A., Carlisle, C.D. & Hawiger, J. (1993) *Proc. Natl. Acad. Sci. USA* **90**, 9887-9891.

Pugin, J., Schurer-Maly, C.-C., Leturcq, D., Moriarty, A., Ulevitch, R. J. & Tobias, P.S. (1993) *Proc. Natl. Acad. Sci. USA* **90**, 2744-2748.

Arditi, M., Zhou, J., Dorio, R., Rong, G.W., Goyert, S.M. & Kim, K.S. (1993) *Infect. Immun.* **61**, 3149-3156.

Copies of these documents are included in the Appendix to this response, which were *de facto* cited in the most recent office action insofar as the foregoing quotation from Diamond *et al.* was incorporated into the action.

The abstract of Goldblum *et al.* thus states "these data thus suggest the LBP and sCD14 each independently functions as an *accessory molecule for LPS* ..." (emphasis added)

The abstract of Read *et al.* states that "the role of sCD14 in HUVEC (human umbilical vein endothelial cells) activation by LPS was established by (i) the blocking effect of monoclonal anti-CD14 antibodies which discriminate between cell-bound and sCD14, (ii) the lack of the serum-enhancing effect after immunodepletion of sCD14, and (iii) establishing a reconstituted system in which recombinant sCD14 was sufficient to

enhance the effects of LPS in the absence of serum and without a requirement for LBP. Thus, this mechanism of endothelial cell *activation by LPS involves a cell-free pool of sCD14* ..." (emphasis added)

The abstract of Pugin *et al.* states "another form of CD14, without the lipid tail, circulates as a soluble plasma protein. In the work we show that soluble CD14 (sCD14) is required for activation of endothelial and epithelial cells by LPS." In the second paragraph of the second column of the article, Pugin *et al.* state "importantly, evidence is provided for a specific mechanism of LPS stimulation of endothelial and epithelial cells that involves LBP and sCD14 and provides an explanation for the serum requirement displayed by both cell types. These data suggest that *LBP and sCD14 in blood or in extravascular fluids may contribute to the consequences of endotoxemia by enabling LPS stimulation* of endothelial and epithelial cells." (emphasis added) A proposed mechanism of action is shown in Figure 7 on page 2748 of the article.

The abstract of Arditi *et al.* states that "serum soluble CD14 represents a naturally occurring *agonist of EC (endothelial cell) responses to LPS*." (emphasis added)

None of these references suggests any role for sCD14 independent of its partnering with LPS in inducing defensin expression, nor does any of these references suggest any reason for administering sCD14 so as to expose epithelial cells to sCD14.

To summarize, the prior art teaches: (i) in the presence of LPS, non-epithelial CD14 can bind thereto to attenuate stimulation of defensin expression or to activate epithelial cells, and (ii) in the absence of LPS, no role for CD14 in stimulation of defensin expression. Withdrawal of the rejection of claims under 35 USC § 103 is thus respectfully requested.

In the event that any official wishes to telephone, the call should be directed to the undersigned at (416) 865-8121 with any proposal to advance prosecution.

Yours very truly,

April 19, 2004
Date

John C. Hunt
Registration No. 36,424

Torys LLP (Customer No. 33,721)
Suite 3000
79 Wellington Street West
Box 270, TD Centre
Toronto, Ontario
M5L 1A9
Canada